Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials

Raffaele Piccolo, Kaare H Bonaa, Orestis Efthimiou, Olivier Varenne, Andrea Baldo, Philip Urban, Christoph Kaiser, Wouter Remkes, Lorenz Räber, Adam de Belder, Arnoud W J van 't Hof, Goran Stankovic, Pedro A Lemos, Tom Wilsgaard, Jörg Reifart, Alfredo E Rodriguez, Expedito E Ribeiro, Patrick W J C Serruys, Alex Abizaid, Manel Sabaté, Robert A Byrne, Jose M de la Torre Hernandez, William Wijns, Peter Jüni, Stephan Windecker, Marco Valgimigli, on behalf of the Coronary Stent Trialists' Collaboration

Summary

Background New-generation drug-eluting stents (DES) have mostly been investigated in head-to-head non-inferiority trials against early-generation DES and have typically shown similar efficacy and superior safety. How the safety profile of new-generation DES compares with that of bare-metal stents (BMS) is less clear.

Methods We did an individual patient data meta-analysis of randomised clinical trials to compare outcomes after implantation of new-generation DES or BMS among patients undergoing percutaneous coronary intervention. The primary outcome was the composite of cardiac death or myocardial infarction. Data were pooled in a one-stage random-effects meta-analysis and examined at maximum follow-up and a 1-year landmark. Risk estimates are reported as hazard ratios (HRs) with 95% CIs. This study is registered in PROSPERO, number CRD42017060520.

Findings We obtained individual data for 26 616 patients in 20 randomised trials. Mean follow-up was 3·2 (SD 1·8) years. The risk of the primary outcome was reduced in DES recipients compared with BMS recipients (HR 0·84, 95% CI 0·78–0·90, p<0·001) owing to a reduced risk of myocardial infarction (0·79, 0·71–0·88, p<0·001) and a possible slight but non-significant cardiac mortality benefit (0·89, 0·78–1·01, p=0·075). All-cause death was unaffected (HR with DES 0·96, 95% CI 0·88–1·05, p=0·358), but risk was lowered for definite stent thrombosis (0·63, 0·50–0·80, p<0·001) and target-vessel revascularisation (0·55, 0·50–0·60, p<0·001). We saw a time-dependent treatment effect, with DES being associated with lower risk of the primary outcome than BMS up to 1 year after placement. While the effect was maintained in the longer term, there was no further divergence from BMS after 1 year.

Interpretation The performance of new-generation DES in the first year after implantation means that BMS should no longer be considered the gold standard for safety. Further development of DES technology should target improvements in clinical outcomes beyond 1 year.

Funding Bern University Hospital.

Lancet 2019; 393: 2503–10

Published **Online** May 2, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30474-X

This online publication has been corrected. The corrected version first appeared at thelancet.com on June 4, 2019

See **Comment** page 2472

Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy (R Piccolo MD); **Department of Community Medicine, University of Tromsø-Arctic University of Norway, Tromsø, Norway** (Prof K H Bonaa MD, T Wilsgaard PhD); **Institute of Social and Preventive Medicine** (O Efthimiou PhD) **and Department of Cardiology, Bern University Hospital** (A Baldo MD, L Räber MD, Prof S Windecker MD, Prof M Valgimigli MD), **University of Bern, Bern, Switzerland; Department of Cardiology, Hôpital Cochin, AP-HP, Paris, France** (O Varenne MD); **Université Paris Descartes, Faculté de Médecine, Paris, France** (O Varenne); **Hôpital de la Tour, Geneva, Switzerland** (P Urban MD); **Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland** (Prof C Kaiser MD); **Department of Cardiology, Sussex Cardiac Centre, Brighton and Sussex University Hospitals, Brighton, UK** (Prof A de Belder MD); **Department of Cardiology, Isala Heart Centre, Zwolle, Netherlands** (W Remkes MD, Prof A W J van 't Hof MD); **Department of Cardiology, Maastricht University Medical Center, Netherlands** (Prof A W J van 't Hof); **Department of Cardiology, Zuyderland Medical Centre Heerlen, Netherlands** (Prof A W J van 't Hof);

Introduction

Percutaneous coronary intervention for the treatment of obstructive coronary artery disease is the most commonly performed cardiovascular procedure and one of the most frequent interventions in medicine. Drug-eluting stents (DES) use antiproliferative agents that inhibit neointimal hyperplasia to reduce the risk of restenosis. These devices have broadened eligibility for percutaneous coronary intervention and increased the number of lesion subsets that can be treated.[1]

Early-generation DES released sirolimus or paclitaxel and were associated with similar risks of death and myocardial infarction as bare-metal stents (BMS), but with an increased, albeit small, risk of stent thrombosis beyond 1 year after implantation.[2,3] Later platforms for DES were aimed at improving safety and efficacy. New-generation DES reduced the risk of stent thrombosis compared with earlier versions while retaining greater efficacy than BMS in limiting the risk of repeat revascularisation.[4] Evidence from randomised clinical trials assessed in network meta-analyses suggests that new-generation DES might also decrease the risk of stent thrombosis compared with BMS.[5,6] Most assessments of new-generation DES, however, have been head-to-head non-inferiority comparisons with early-generation DES, and whether they improve outcomes other than stent thrombosis and repeat revascularisation compared with BMS remains unclear. BMS continue to be used in a sizeable proportion (around 20%) of patients worldwide.[7] We did an individual patient data meta-analysis to investigate outcomes for new-generation DES compared with BMS.

Methods

The protocol was developed according to the guidelines of the Preferred Reporting Items for a Systematic

Department of Cardiology, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia (G Stankovic MD); **Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil** (P A Lemos MD, Prof E E Ribeiro MD); **Department of Cardiology, Kerckhoff Klinik, Bad Nauheim, Germany** (J Reifart MD); **Cardiac Unit, Cardiology Fellow Training Program, Otamendi Hospital, Buenos Aires School of Medicine, Buenos Aires, Argentina** (Prof A E Rodriguez MD); **International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College, London, London, UK** (Prof P W J C Serruys MD); **Department of Invasive Cardiology, Institute Dante Pazzanese of Cardiology, São Paulo, Brazil** (A Abizaid MD); **Cardiology Department, Cardiovascular Institute (ICCV), Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain** (Prof M Sabaté MD); **Deutsches Herzzentrum München, Technische Universität München, Munich, Germany** (R A Byrne PhD); **German Centre for Cardiovascular Research (DZHK), Munich, Germany** (R A Byrne); **Munich Heart**

Research in context

Evidence before this study

We searched PubMed, Embase, and three websites (www.tctmd.com, www.escardio.org, and www.cardiosource.com) without language restrictions for randomised trials reported up to Dec 19, 2017, that compared new-generation drug-eluting stents (DES) with bare-metal stents (BMS) in patients undergoing percutaneous coronary intervention. We used search terms "stents", "drug-eluting stents", "percutaneous coronary intervention", and "random*". Trials were included if at least 90% of patients in the DES group received new-generation stents. Most of the evidence supporting the use of new-generation DES for percutaneous coronary intervention showed superiority to earlier-generation DES or non-inferiority between different types of new-generation DES. Little evidence was available from head-to-head comparisons of new-generation DES and BMS and did not reveal whether new-generation DES improve clinical prognostically relevant outcomes, such as myocardial infarction or cardiac death. Only two studies have shown reduced risk of myocardial infarction with new-generation DES compared with BMS. Almost all trials included repeat revascularisation procedures in the primary endpoint and, therefore, provide imprecise estimates for less common prognostic factors. We identified 20 trials eligible for the study for which we requested and obtained individual patient data.

Added value of this study

In this individual patient data meta-analysis of randomised clinical trials, we found that new-generation DES reduced the composite primary outcome, risk of cardiac death or myocardial infarction, compared with BMS. Additionally, we found reductions in myocardial infarction, definite stent thrombosis, and target-vessel revascularisation. Cardiac death was numerically lower with DES than BMS, but did not reach significance. We identified a time-dependent effect on adverse events with new-generation DES, including cardiac death, up to 1 year after placement but without further incremental benefit or loss thereafter. Implantation of DES in the left anterior descending artery was associated with greater relative risk reduction for the primary endpoint than other locations.

Implications of all the available evidence

Use of new-generation DES improves efficacy and safety compared with BMS. This benefit is gained early after percutaneous coronary intervention and is maintained long term. The meta-analysis provides strong evidence that BMS should no longer be considered the gold standard for safety.

Review and Meta-analysis of Individual Participant Data Development Group.[8]

Search strategy and eligibility assessment

We did a meta-analysis of individual patient data from randomised clinical trials that compared new-generation DES with BMS in patients undergoing percutaneous coronary intervention for coronary artery disease. We defined new-generation DES as any DES subsequent to the Cypher sirolimus-eluting stent (Cordis, Miami Lakes, FL, USA) and the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, MA, USA). Eligible trials had used new-generation stents in at least 90% of patients in the DES group. Two investigators (RP and AB) assessed trial eligibility criteria and a third investigator (MV) could be consulted if eligibility could not be agreed. Randomised trials reported up to Dec 19, 2017, were identified by systematic searches of PubMed, Embase, and three websites (www.tctmd.com, www.escardio.org, and www.cardiosource.com; appendix) without language restrictions. Reference lists of retrieved articles were searched for additional trials.

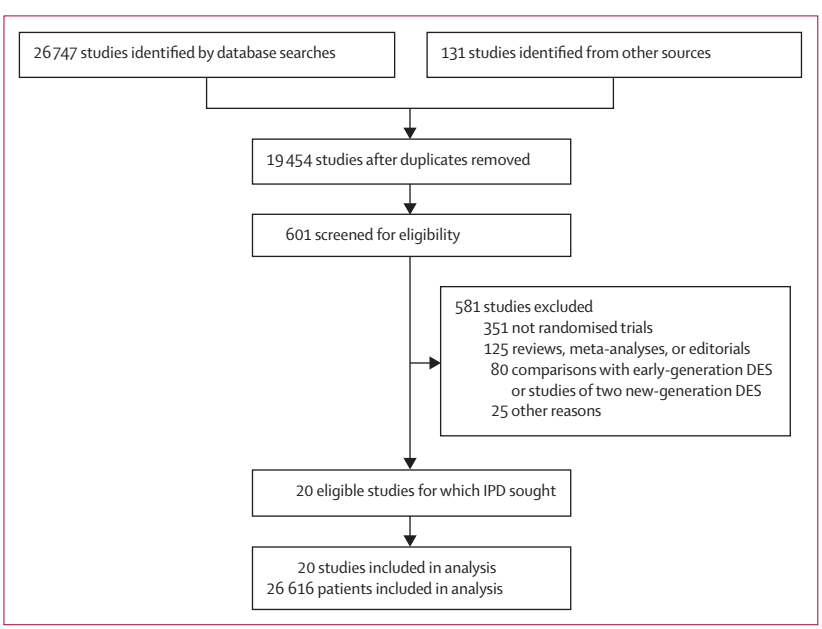

Figure 1: **Trial profile**
DES=drug-eluting stents. IPD=individual patient data.

Data collection and quality assessment

We contacted the principal investigators of eligible trials to request data at the patient level in anonymised electronic datasets (appendix). Data for five randomised trials were already available from a previous study.[9] We checked data for completeness and consistency and compared them with the results of the original publications. The principal investigators of the included trials were contacted in case of missing data or if questions arose during the integrity checks. Once queries had been resolved, the clean data were uploaded to the main study dataset. Two investigators (RP and AB) independently assessed the quality of included trials with the Cochrane Collaboration's tool for

assessing risk of bias. Disagreements were resolved first by discussion and, if necessary, by consulting a third author (MV) for arbitration. Each trial had been approved by its local medical ethics committee and all patients had provided written informed consent.

Outcomes

The prespecified composite primary outcome in this meta-analysis was cardiac death or myocardial infarction. Secondary outcomes were all-cause death, cardiac death, myocardial infarction, definite stent thrombosis, and target-vessel revascularisation. Outcomes were analysed at the longest available follow-up in the primary analysis, at 5 years of follow-up, and at 30-day and 1-year landmarks.

Data analysis

Continuous variables were summarised by their means and SDs across all included patients. The two treatment groups were compared with ANOVA stratified by trial. Categorical variables were summarised by the corresponding counts and percentages and were compared with the Cochran-Mantel-Haenszel test stratified by trial.

All outcomes were analysed with time-to-event analyses. We first summarised the data with unadjusted Kaplan-Meier estimates at the longest available follow-up then did a series of random-effects meta-analyses of individual patient data. All analyses were done by intention to treat. Pooled risk estimates were expressed as hazard ratios (HRs) with 95% CIs. For the primary analysis, we used a one-stage meta-analysis model[10] for which we synthesised individual patient data from all trials simultaneously while preserving the random allocations in the original trials. In sensitivity analyses we used a two-stage approach and analysed the data from each study independently with a Cox regression model. We then combined the study-specific logarithms of the HRs and the corresponding SEs at the second stage with the DerSimonian-Laird random-effects model and using the Hartung-Knapp variance estimator.[11] We also did a one-stage fixed-effect analysis with a Cox regression model stratified by trial.

For the one-stage meta-analysis of individual patient data we assessed the extent of heterogeneity by assessing the estimated SD of random effects (τ). For the two-stage meta-analysis we visually inspected the forest plots and calculated the I^2 statistic.[12] To account for τ in the uncertainty around the pooled risk estimates, we calculated 95% prediction intervals for HRs.[13] The number needed to treat for benefit was derived from the inverse of the absolute risk reduction. We did a landmark analysis by setting 1 year as the landmark and derived the p value of the interaction for effect modification by period (appendix).[14]

Possible sources of heterogeneity in treatment effect were explored by assessing the effects of prespecified variables on the primary outcome with a one-stage individual patient data meta-analysis model with treatment-covariate interactions (appendix).[15] We fitted a separate model for each covariate. The prespecified variables were age (analysed as a continuous variable),

	Drug-eluting stents (n=14 070)	Bare-metal stents (n=12 546)	p value
Age (years)	65·7 (12·3)	66·3 (12·4)	0·458
Sex	..	..	0·067
Men	10 542/14 069 (74·9%)	9269/12 543 (73·9%)	..
Women	3527/14 069 (25.1%)	3274/12 543 (24.1%)	..
Smokers	4277/13 654 (31·3%)	3809/12 149 (31·4%)	0·092
Hypertension	8259/14 029 (58·9%)	7324/12 500 (58·6%)	0·156
Hyperlipidaemia	7904/13 731 (57·6%)	6974/12 208 (57·1%)	0·208
Diabetes	2740/14 046 (19·5%)	2344/12 525 (18·7%)	0·069
Insulin-treated	446/2677 (16·7%)	378/2323 (16·3%)	0·426
Previous MI	2143/14 025 (15·3%)	2007/12 505 (16·0%)	0·548
Previous PCI	1901/9950 (19·1%)	1806/8507 (21·2%)	0·074
Previous CABG	905/14 060 (6·4%)	1004/12 541 (8·0%)	0·605
Indication for PCI			
Stable CAD	4047/13 927 (29·1%)	3644/12 408 (29·4%)	0·907
Unstable angina	1959/14 012 (14·0%)	1871/12 478 (15·0%)	0·956
Non-ST-segment elevation MI	3479/13 975 (24·9%)	3164/12 462 (25·4%)	0·636
ST-segment elevation MI	4105/13 922 (29·5%)	3427/12 406 (27·6%)	0·522
Glycoprotein IIb/IIIa receptor inhibitors	2781/12 344 (22·5%)	2378/11 020 (21·6%)	0·420
Multivessel disease	5837/13 517 (43·2%)	4968/11 993 (41·4%)	0·239
Number of implanted stents	1·6 (1·0)	1·6 (1·0)	0·391
Total stent length (mm)	28·4 (19·5)	26·9 (18·2)	<0·001
Mean stent diameter (mm)	3·3 (0·5)	3·3 (0·6)	<0·001
Overlapping stent	2395/13 403 (17·9%)	2152/11 877 (18·1%)	0·201
Number of stented segments	..	..	0·088
0	5/14 052 (<1·0%)	5/12 524 (<1·0%)	..
1	10 297/14 052 (73·3%)	9231/12 524 (73·7%)	..
2	2758/14 052 (19·6%)	2480/12 524 (19·8%)	..
3	751/14 052 (5·3%)	608/12 524 (4·9%)	..
4	188/14 052 (1·3%)	141/12 524 (1·1%)	..
5	40/14 052 (<1·0%)	52/12 524 (<1·0%)	..
6	10/14 052 (<1·0%)	6/12 524 (<1·0%)	..
7	3/14 052 (<1·0%)	1/12 524 (<1·0%)	..
Target-vessel location			
Left main artery	1022/13 968 (7·3%)	591/12 463 (4·7%)	0·499
Left anterior descending artery	6476/13 968 (46·4%)	5805/12 463 (46·6%)	0·859
Left circumflex artery	4047/13 968 (29·0%)	3433/12 463 (27·5%)	0·51
Right coronary artery	5260/13 968 (37·7%)	4674/12 462 (37·5%)	0·279
Thin-strut stent (<100 μm)	11 198/14 046 (79·7%)	10 681/12 526 (85·3%)	<0·001
Type of $P2Y_{12}$ receptor inhibitor	..	..	0·919
None	1/12 123 (<1·0%)	3/10 814 (<1·0%)	..
Clopidogrel	10 726/12 123 (84·8%)	10 217/10 814 (90·0%)	..
Ticagrelor	89/12 123 (<1·0%)	63/10 814 (<1·0%)	..
Prasugrel	1837/12 123 (14·5%)	1069/10 814 (9·4%)	..
Duration of DAPT (days)	291·7 (180·4)	244·2 (175·9)	<0·001

Data are mean (SD) or n/N (%). MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. CAD=coronary artery disease. DAPT=dual antiplatelet therapy.

Table 1: **Baseline and procedural characteristics**

	Drug-eluting stents (n=14 070)	Bare-metal stents (n=12 546)	Hazard ratio (95% CI)	p value	τ
Longest available follow-up					
Cardiac death or MI	1371 (14·5%)	1472 (16·7%)	0·84 (0·78–0·90)	<0·001	0·003
All-cause death	1031 (11·0%)	996 (12·0%)	0·96 (0·88–1·05)	0·358	0·004
Cardiac death	494 (4·8%)	503 (5·8%)	0·89 (0·78–1·01)	0·075	0·003
MI	1020 (11·7%)	1124 (13·6%)	0·79 (0·71–0·88)	<0·001	0·070
Target-vessel revascularisation	920 (9·6%)	1448 (15·0%)	0·55 (0·50–0·60)	<0·001	0·003
Definite stent thrombosis	125 (1·2%)	173 (1·7%)	0·63 (0·50–0·80)	<0·001	0·008
5 years of follow-up					
Cardiac death or MI	1345 (12·5%)	1446 (14·2%)	0·83 (0·78–0·90)	<0·001	0·003
All-cause death	1013 (9·8%)	974 (10·4%)	0·95 (0·88–1·05)	0·400	0·004
Cardiac death	490 (4·6%)	492 (4·9%)	0·90 (0·79–1·03)	0·116	0·003
MI	994 (9·6%)	1099 (11·0%)	0·78 (0·72–0·88)	<0·001	0·056
Target-vessel revascularisation	904 (8·4%)	1436 (13·4%)	0·54 (0·50–0·59)	<0·001	0·003
Definite stent thrombosis	123 (1·1%)	171 (1·6%)	0·63 (0·50–0·80)	<0·001	0·008
1-year follow-up					
Cardiac death or MI	829 (6·0%)	989 (8·0%)	0·74 (0·67–0·81)	<0·001	0·003
All-cause death	499 (3·5%)	495 (4·0%)	0·94 (0·81–1·04)	0·197	0·003
Cardiac death	301 (2·2%)	331 (2·7%)	0·82 (0·70–0·96)	0·016	0·003
MI	591 (4·3%)	746 (6·0%)	0·69 (0·62–0·78)	<0·001	0·070
Target-vessel revascularisation	547 (4·0%)	1073 (8·8%)	0·43 (0·39–0·48)	<0·001	0·015
Definite stent thrombosis	83 (0·6%)	137 (1·1%)	0·52 (0·40–0·69)	<0·001	0·008

MI=myocardial infarction.

Table 2: **Results of one-stage meta-analysis.**

Alliance, Munich, Germany (R A Byrne); **Hospital Marqués de Valdecilla, Santander, Spain** (J M de la Torre Hernandez MD); **Lambe Institute for Translational Medicine, Galway, Ireland** (Prof W Wijns MD); **Cúram, Biomedical Sciences, National University of Ireland Galway, Galway, Ireland** (Prof W Wijns); **and Applied Health Research Centre of the Li Ka Shing Knowledge Institute, Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, ON, Canada** (Prof P Jüni MD)

Correspondence to: Prof Marco Valgimigli, Department of Cardiology, Bern University Hospital University of Bern, 3010 Bern, Switzerland
marco.valgimigli@insel.ch

See Online for appendix

For the **Cochrane Collaboration's tool** see https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

sex, diabetes, clinical presentation at the time of percutaneous coronary intervention, multivessel disease, stent placement in the left anterior descending artery, overlapping stents, number of implanted stents, mean stent diameter, use of glycoprotein IIb/IIIa receptor inhibitors, and use of newer $P2Y_{12}$ receptor inhibitors (ticagrelor or prasugrel). In a sensitivity analysis we also fitted an individual patient data model that separated the within-trial and across-trial treatment-covariate interactions to avoid ecological bias.[15]

All p values were based on two-sided tests and the threshold for significance was 0·05 in all analyses. We used Stata Statistical Software version 14 and R version 3.2.1 for all statistical analyses.

We did sensitivity analyses from which we excluded patients who received early-generation DES or thick-strut BMS (thickness >100 μm). A landmark analysis with two timepoints (30 days and 365 days) was also done to appraise the differential contribution of very early stent failure events, particularly thrombotic events, as opposed to those occurring in between 30 days and 1 year, which are generally related to an abnormal healing process leading to neointimal hyperplasia (appendix). This study was registered with PROSPERO, number CRD42017060520.

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

We screened 19 454 unique citations. Of these, 601 were judged to be potentially eligible by screening of titles and abstracts, and after full-text review 20 were deemed eligible (figure 1). Individual patient data were sought and obtained for all 20 studies, which therefore contributed to the meta-analysis (appendix). Trial characteristics, populations of patients, and the definitions used for outcomes are described in the appendix. We obtained data for 26 616 participants of whom 14 070 (53%) had been assigned to receive DES and 12 546 (47%) to receive BMS. Baseline clinical characteristics were largely balanced between the two study groups (table 1). Slightly more men than women were allocated to DES than BMS, and BMS tended to have larger diameters and shorter lengths than DES. Trials were generally judged to have low risk of bias, although treatment was masked for patients and physicians in only four trials (appendix).

Most patients received thin-strut stents, although these were less frequently implanted in the DES group than in the BMS group (table 1). Among patients who received DES, 7526 (53·5%) of 14 070 received everolimus-eluting stents, 2407 (17·1%) received zotarolimus-eluting stents, 2641 (19·3%) received biolimus-eluting stents, and 375 (2·8%) received sirolimus-eluting stents (appendix). Early-generation DES were implanted in 1·4% of patients. In the BMS group, about 80% of patients received seven of the 21 different devices used (appendix). Duration of dual antiplatelet therapy was on average 50 days longer after DES than BMS (table 1).

The maximum length of follow-up ranged from 1 to 6 years (mean 3·2 [SD 1·8] years, median 2·1, IQR 1·9–4·9). The duration was 2 years or more in 14 trials and at least 5 years in six trials. Ten trials reported non-industry sponsorship (appendix).

At longest available follow-up, the risk of the primary outcome of cardiac death or myocardial infarction was significantly improved in the DES compared with the BMS group (14·5% *vs* 16·7%, HR 0·84, 95% CI 0·78–0·90, p<0·0001; table 2, figure 2). The number needed to treat for benefit was around 46. DES were associated with a reduced risk of myocardial infarction compared with BMS, whereas DES and BMS did not differ for cardiac death or all-cause death (table 2, figure 2). Compared with BMS, DES were associated with reduced risk of definite stent thrombosis and target-vessel revascularisation (table 2, figure 2). Risk estimates for primary and secondary outcomes at 5 years of follow-up were consistent with those observed at time of longest follow-up (table 2).

In the landmark analysis, for the primary outcome we saw significant heterogeneity in the treatment effects of DES and BMS before and after 1 year ($p_{interaction}$<0·0001).

Compared with BMS, DES were associated with reduced risk of cardiac death or myocardial infarction up to but not beyond 365 days (figure 3, appendix). DES use was also associated with reduced risks of all the secondary outcomes up to 1 year with no detectable change in treatment effect thereafter (figure 3, appendix). In the sensitivity analysis with two landmark timepoints, DES were associated with reduced risks in the first 30 days and from 31 to 365 days for the primary outcome and the secondary outcomes myocardial infarction, definite stent thrombosis, and target-vessel revascularisation (appendix).

DES consistently improved the primary outcome at the longest available follow-up for all subgroups with a quantitative interaction for target-vessel location (figure 4). There was strong evidence that DES lower the risk of cardiac death or myocardial infarction among patients undergoing stent implantation in the left anterior descending artery, but more modest effects were seen in other coronary vessels.

We did not find clinically important heterogeneity in any meta-analyses. At the longest follow-up we found moderate heterogeneity for myocardial infarction that led to a non-significant prediction interval (appendix).

The main results of the individual patient data meta-analysis remained consistent with the two-stage random-effects approach and the one-stage fixed-effect approach (appendix). Results for primary and secondary outcomes remained unchanged after excluding 115 patients who had received the Cypher DES, 90 patients who had received the Taxus DES, and 1838 patients who received thick-strut BMS (appendix). In a sensitivity analysis, we fitted a model including within-study and across-study interactions between treatment and target-vessel location. Results were similar to those obtained by the model including only a within-studies interaction ($p_{interaction}$=0·018).

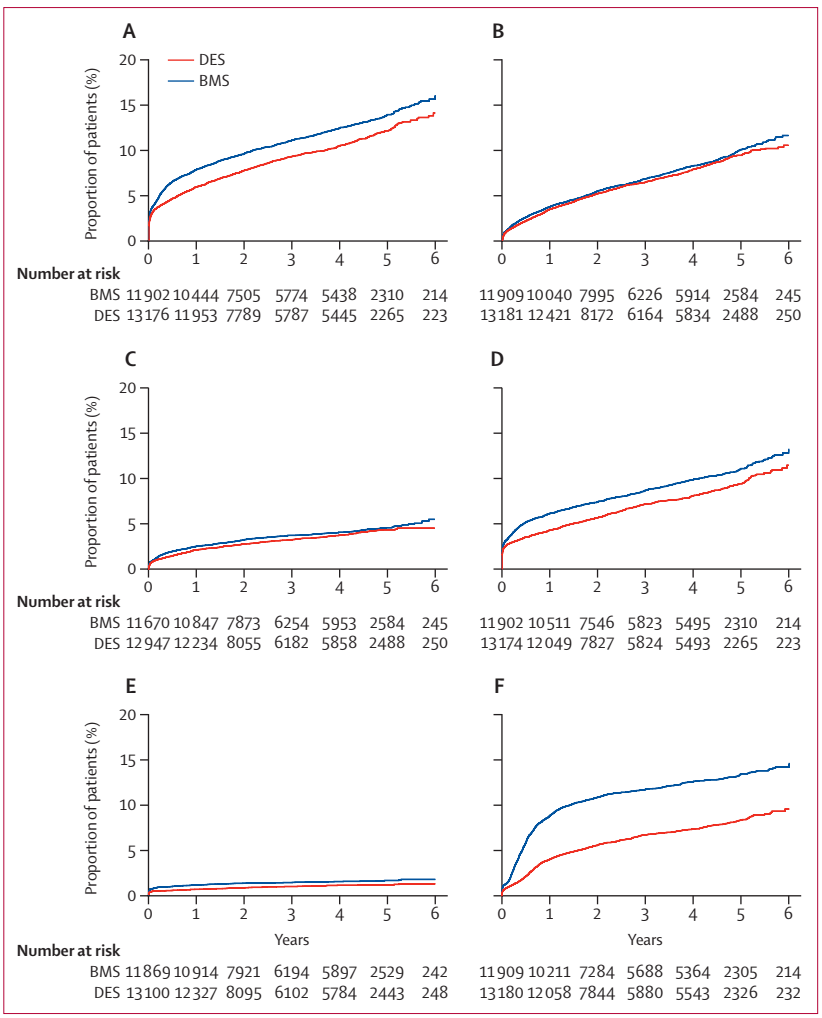

Figure 2: **Outcomes at longest follow-up**
(A) Cardiac death or myocardial infarction (primary outcome). (B) All-cause death. (C) Cardiac death. (D) Myocardial infarction. (E) Definite stent thrombosis. (F) Target-vessel revascularisation. BMS=bare-metal stents. DES=new-generation drug-eluting stents.

Discussion

The data we obtained from randomised clinical trials yielded strong evidence that use of DES reduced the risk of cardiac death or myocardial infarction compared with BMS at the mean follow-up time of 3·2 years and at 5 years. This benefit was mainly due to a decreased risk of myocardial infarction in recipients of DES compared with BMS. The use of DES was also associated with a significantly reduced risk of definite stent thrombosis and target-vessel revascularisation at the longest available follow-up and at 5 years.

Introduced in 2002, DES represented a paradigm shift in the treatment of patients undergoing percutaneous coronary intervention by greatly lessening the need for repeat revascularisation compared with BMS. However, safety concerns were raised due to an excess of very late (>1 year) thrombotic events with early-generation DES. New-generation DES included a broad range of refinements, including the use of lower antiproliferative drug loads, the omission of paclitaxel as antiproliferative agent, thinner metallic stent struts, more biocompatible durable or biodegradable polymers, and polymer-free stents. Nevertheless, controversy remains as to whether these devices affect prognostically relevant endpoints, such as death or myocardial infarction.

In the Clinical Evaluation of the Xience-V Stent in Acute Myocardial Infarction Trial,[16] which included 1498 patients with acute myocardial infarction, the risk of all-cause death was significantly reduced with DES compared with BMS at 5 years of follow-up. This difference was mainly related to a decrease in non-cardiac fatalities. It was speculated that DES prevented stent thrombosis and repeat revascularisation, leading to fewer readmissions to hospital and other complications, including infections and sepsis, which were the second major cause of non-cardiac death in the trial.[16] Conversely, the Norwegian Coronary Stent Trial,[17] which included

	DES (%) (n=14 070)	BMS (%) (n=12 546)	HR (95%CI)	p value	$p_{interaction}$
Cardiac death or myocardial infarction					
Overall	1371 (14·5%)	1472 (16·7%)	0·84 (0·78–0·90)	<0·001	<0·001
0–365 days	829 (6·0%)	989 (8·0%)	0·74 (0·67–0·81)	<0·001	
>365 days	542 (9·1%)	483 (9·5%)	1·04 (0·92–1·18)	0·490	
All-cause death					
Overall	1031 (11·0%)	996 (12·0%)	0·96 (0·88–1·05)	0·358	0·368
0–365 days	499 (3·6%)	495 (4·0%)	0·92 (0·81–1·04)	0·197	
>365 days	532 (7·7%)	501 (8·3%)	1·00 (0·88–1·13)	1·00	
Cardiac death					
Overall	494 (4·8%)	503 (5·8%)	0·89 (0·78–1·01)	0·075	0·079
0–365 days	301 (2·2%)	331 (2·7%)	0·82 (0·70–0·96)	0·016	
>365 days	193 (2·6%)	172 (3·1%)	1·03 (0·84–1·26)	0·794	
Myocardial infarction					
Overall	1020 (11·7%)	1124 (13·6%)	0·79 (0·71–0·88)	<0·001	<0·001
0–365 days	591 (4·3%)	746 (6·0%)	0·69 (0·62–0·78)	<0·001	
>365 days	429 (7·7%)	378 (8·0%)	1·06 (0·93–1·22)	0·384	
Definite stent thrombosis					
Overall	125 (1·2%)	173 (1·7%)	0·63 (0·50–0·80)	<0·001	<0·001
0–365 days	83 (1·0%)	137 (1·1%)	0·52 (0·40–0·69)	<0·001	
>365 days	42 (1·0%)	36 (1·0%)	1·07 (0·68–1·68)	0·764	
Target-vessel revascularisation					
Overall	920 (9·6%)	1448 (15·0%)	0·55 (0·50–0·60)	<0·001	<0·001
0–365 days	547 (4·0%)	1073 (8·8%)	0·43 (0·39–0·48)	<0·001	
>365 days	373 (5·8%)	375 (6·8%)	0·88 (0·76–1·01)	0·077	

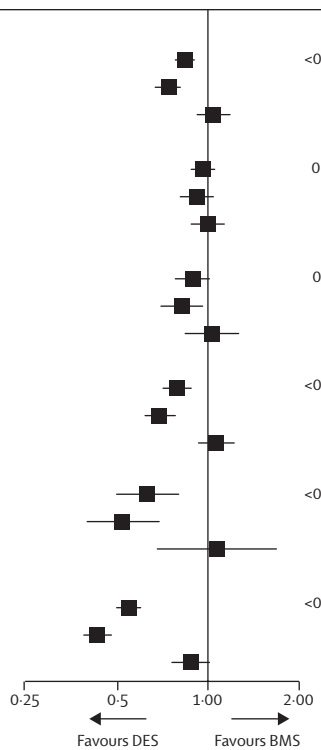

Figure 3: **Outcomes in 1-year landmark analysis**
The p values for interaction are calculated for 0–365 days versus after 365 days based on the HRs and 95% CIs. BMS=bare-metal stents. DES=new-generation drug-eluting stents. HR=hazard ratio.

9013 patients, found no benefit with DES for all-cause or cardiac mortality or for myocardial infarction. Nevertheless, the risk of definite stent thrombosis was reduced by 36% with DES compared with BMS.

The perceived greater safety and lower cost of BMS compared with new-generation DES mean that BMS continue to be implanted in 20% of patients aged 65 years or older undergoing percutaneous coronary interventions.[7] While European Society of Cardiology guidelines no longer recommended the use of BMS,[18] a similar position has not been taken by the American College of Cardiology and American Heart Association, whose latest guidelines were published in 2011.[19]

Our individual patient data meta-analysis provides robust evidence that the use of DES reduced the risk of myocardial infarction by 21% compared with BMS. This finding is important because in only two of the 20 trials we analysed had this outcome been significantly reduced.[20,21] Of note, those two studies recruited mainly[20] or exclusively[21] patients deemed to be at high risk of bleeding and mandated dual antiplatelet therapy for 1 month irrespective of the stent used. Hence, the argument that DES implantation lowers the frequency of myocardial infarction because of concomitant longer duration of dual antiplatelet therapy than in BMS recipients seems invalid. The decreased hazard of myocardial infarction with DES is biologically plausible given the concurrent reductions in stent thrombosis and target-vessel revascularisation. The clinical correlate in more than 90% of patients with stent thrombosis or myocardial infarction is death,[22] and roughly a third of patients with in-stent restenosis who need repeat revascularisation in a target vessel are admitted with acute coronary syndrome.[23] Furthermore, restenosis after coronary stenting has been associated with increased risk of mortality in cohorts undergoing angiographic surveillance.[24] Even elective and uncomplicated revascularisation in the targe vessel is associated with an increased risk of mortality, partly due to increased risk of myocardial infarction following repeat revascularisation procedures.[25]

We found no evidence that the use of DES affects all-cause mortality, and cardiac deaths were only marginally (and non-significantly) lower with DES than with BMS at the longest available follow-up. In our individual patient data analysis, 2027 fatal events were included among which only 997 (49·2%) were from cardiac causes. Thus, deaths among patients undergoing percutaneous coronary intervention were due mainly to non-cardiac causes, particularly during longer-term

follow-up, and were unlikely to be preventable by a specific type of coronary stent. These findings align well with registry data from the past two decades that have shown pronounced temporal switches from predominantly cardiac to predominantly non-cardiac causes of death after percutaneous coronary intervention.[26]

As well as the primary outcomes, we identified significant time-dependent treatment effects on myocardial infarction, definite stent thrombosis, and target-vessel revascularisation. The risk of cardiac death was also significantly reduced in DES recipients in the first year after implantation, but interaction testing was not significant. It seems plausible that an early cardiac mortality benefit diminishes over time due to non-stent related fatalities.

The observation that beneficial effects of DES on safety endpoints, including myocardial infarction and definite stent thrombosis, accrued only within the first year after treatment, even within 30 days, with no further incremental benefit or loss thereafter deserves particular attention. First, it suggests that contemporary DES technology is less prone to early thrombotic events after implantation and confirms the reduced risk of non-fatal ischaemic events associated with a fall in intimal hyperplasia compared with in BMS recipients. Second, it supports the resolution of long-term safety issues seen with early-generation DES. Third, outperformance in the primary endpoint of BMS by contemporary DES technology in the first year after implantation without further comparative improvements means that BMS should no longer be considered the gold standard for safety. The focus of future DES technology should target clinical outcome improvements beyond 1 year.

A further strength of this individual patient data meta-analysis was the opportunity to explore the treatment effects of DES compared with BMS across several subgroups. We found no interaction between the primary outcome and any patient or lesion characteristic except for target-vessel location. The primary outcome was reduced most with DES than BMS among patients who underwent percutaneous coronary intervention in the left anterior descending artery with no difference between stent types for other locations. The myocardial territory supplied by the left anterior descending artery is larger than other vessels (45–55% of the left ventricle) and, therefore, this subgroup of patients probably derived greater benefit from the prevention of restenosis and stent thrombosis with DES than with BMS.

The results of this study should be interpreted in view of several limitations. First, there are inherent limitations in patient-level, pooled analyses that reflect the shortcomings of the original studies. Second, although the number of different types of DES was limited and more than 50% of patients received everolimus-eluting stents, a mixture of devices was used in the DES group. Third, a small number of patients received early-generation DES that are associated with poorer safety and efficacy than new-generation DES and are no longer used in clinical practice. Nevertheless, our findings were unchanged after the exclusion of these patients. Fourth, although there was no signal of a difference between DES and BMS beyond 1 year, the mean follow-up in our individual patient data analysis was about 3 years. Longer follow-up is needed to confirm the durability of the observed benefit. Fifth, the effect of stent selection on the type of myocardial infarction could not be assessed because many of the included studies did not collect this information. Finally, we did not adjust or account for post-randomisation covariates, such as actual duration of dual antiplatelet therapy, to avoid violating the principle of randomisation. However, several trials are addressing the efficacy and safety of abbreviated antiplatelet regimens after contemporary percutaneous coronary intervention.[27]

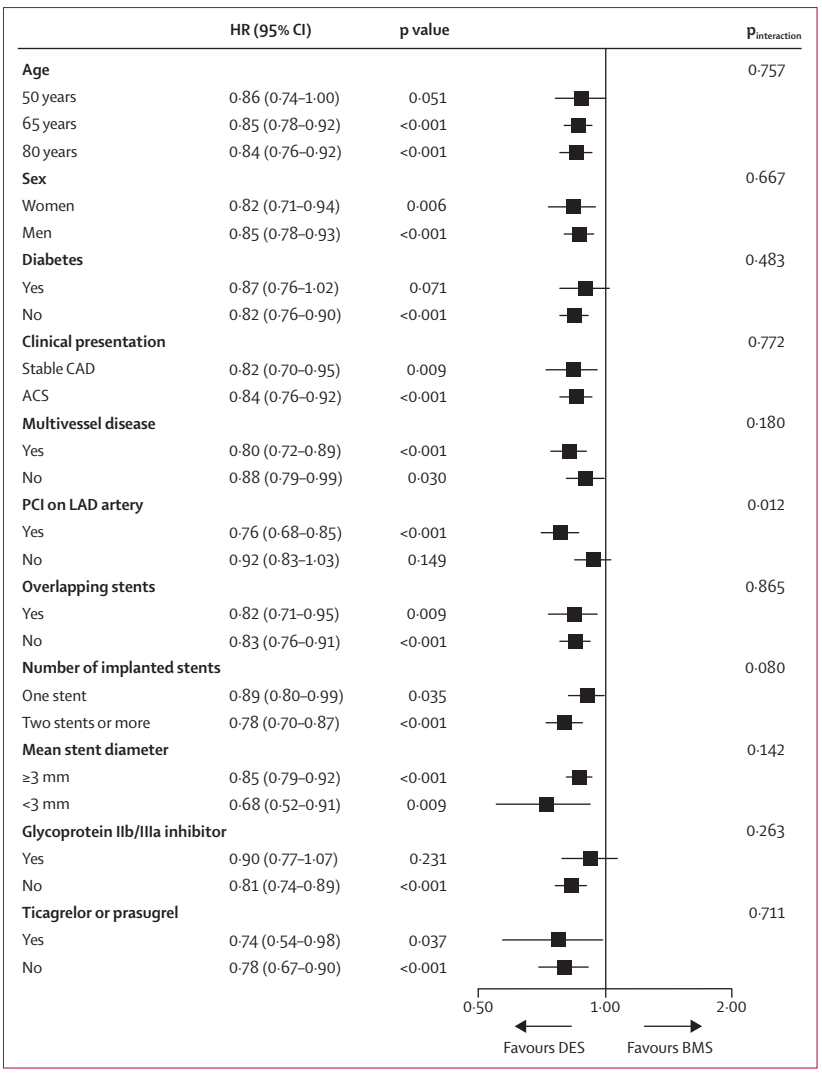

Figure 4: **Subgroup analysis and meta-regressions for the primary outcome**
ACS=acute coronary syndrome. BMS=bare-metal stents. CAD=coronary artery disease. DES=new-generation drug-eluting stents. HR=hazard ratio. LAD=left anterior descending. PCI=percutaneous coronary intervention.

This collaborative meta-analysis, which was based on the totality of available randomised data, showed that the use of new generation DES rather than BMS is associated with a sustained reduction in the risk of cardiac death or myocardial infarction. We identified time-dependent treatment effects that were characterised by reduced risk of the composite endpoint during the first year after implantation without an off-setting effect during the subsequent years.

Contributors

MV conceived and RP, OE, AB, and MV designed the study. RP, OE, and AB analysed the data. RP and MV drafted the Article. All authors interpreted the data and revised and approved the final manuscript.

Declaration of interests

OV has received personal fees from Boston Scientific, Abbott Vascular, AstraZeneca, Biotronik, and Servier, and non-financial support from Biosensors. PU has acted as a consultant to Biosensors, a stent manufacturing company. LR has received personal fees from Abbott Vascular, Amgen, AstraZeneca, Biotronik, CLS Bhering, Regeneron, and Sanofi, and grants from Abbott Vascular, Heartflow, Regenron, and Sanofi. AWJv'tH has received grants from Medtronic. PWJCS has received personal fees from Abbott, Biosensors, Cardialysis, HeartFlow, Medtronic, Philips/Volcano, Sinomedical Sciences, and Xeltis and consultancy fees from Abbott Laboratories, Biosensors, Cardialysis, Heartflow, Medtronic, Philips/Volcano, Sino Medical Sciences Technology, and Xeltis. MS has acted as a consultant to Abbott Vascular, a stent manufacturing company. RAB has received personal fees from B Braun Melsungen, Biotronik, Micell Technologies, grants and personal fees from Boston Scientific, and grants from Celonova Biosciencers. JMdlTH has received unrestricted grants for research from Amgen, Abbott, Biotronik, and Bristol-Myers Squibb and advisory fees from AstraZeneca, Boston scientific, Daichy, and Medtronic. WW has received grants and personal fees from Biotronik , grants from Medtronic, Mi-Cell, Micro-Port, and Terumo, has acted as a medical advisor for Rede Optimus Research, and is cofounder of Argonauts, an innovation facilitator. PJ serves as an unpaid member of steering groups for trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company. SW has received grants from Amgen, Abbott, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude Medical, and Terumo. MV has received grants and personal fees from Abbott, AstraZeneca, and Terumo, personal fees from Alvimedica, Amgen, Bayer, Biosensors, Chiesi, Daiichi, Idorsia, and Sankyo, and grants from Medicure. The other authors declare no competing interests.

References

1 Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. *Lancet* 2015; **386:** 702–13.

2 Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 2005; **293:** 2109–17.

3 Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 2008; **299:** 1788–99.

4 Valgimigli M, Tebaldi M, Borghesi M, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment). *JACC Cardiovasc Interv* 2014; **7:** 20–28.

5 Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; **379:** 1393–402.

6 Kang SH, Chae IH, Park JJ, et al. Stent thrombosis with drug-eluting stents and bioresorbable scaffolds: evidence from a network meta-analysis of 147 trials. *JACC Cardiovasc Interv* 2016; **9:** 1203–12.

7 Rymer JA, Harrison RW, Dai D, et al. Trends in bare-metal stent use in the United States in patients aged ≥65 years (from the CathPCI Registry). *Am J Cardiol* 2016; **118:** 959–66.

8 Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA* 2015; **313:** 1657–65.

9 Valgimigli M, Sabaté M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. *BMJ* 2014; **349:** g6427.

10 Debray TPA, Moons KGM, van Valkenhoef G, et al. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods* 2015; **6:** 293–309.

11 Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med* 2001; **20:** 3875–89.

12 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.

13 IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016; **6:** e010247.

14 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326:** 219.

15 Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Stat Med* 2017; **36:** 772–89.

16 Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet* 2016; **387:** 357–66.

17 Bønaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016; **375:** 1242–52.

18 Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2018; **40:** 87–165.

19 Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; **58:** e44–122.

20 Valgimigli M, Patialiakas A, Thury A, et al. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol* 2015; **65:** 805–15.

21 Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015; **373:** 2038–47.

22 Windecker S, Meier B. Late coronary stent thrombosis. *Circulation* 2007; **116:** 1952–65.

23 Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006; **151:** 1260–64.

24 Cassese S, Byrne RA, Schulz S, et al. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. *Eur Heart J* 2015; **36:** 94–99.

25 Palmerini T, Della Riva D, Biondi-Zoccai G, et al. Mortality following nonemergent, uncomplicated target lesion revascularization after percutaneous coronary intervention: an individual patient data pooled analysis of 21 randomized trials and 32,524 patients. *JACC Cardiovasc Interv* 2018; **11:** 892–902.

26 Spoon DB, Psaltis PJ, Singh M, et al. Trends in cause of death after percutaneous coronary intervention. *Circulation* 2014; **129:** 1286–94.

27 Frigoli E, Smits P, Vranckx P, et al. Design and rationale of the management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus standard DAPT regimen (MASTER DAPT) study. *Am Heart J* 2018; **209:** 97–105.